IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	Confirmation No. 1799
BATTISTINI et al.	Atty. Ref.: 4865-38
Appln. No. 10/812,308	T.C. / Art Unit: 1611
Filed: March 30, 2004	Examiner: C.E. Rae

FOR: USE OF (3-(2-ETHYLPHENYL)-5-METHOXYPHENYL)-1H-[1,2,4]-TRIAZOLE FOR THE TREATMENT OF AUTOIMMUNE DISEASES

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APPEAL BRIEF UNDER 37 CFR § 41.37

April 28, 2009

Mail Stop Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Appellants submit this Brief to appeal the Examiner's final rejections as set forth in his Office Action mailed October 28, 2008 (the "Office Action"). The fee required under 37 CFR § 41.20(b)(2) is submitted herewith.

Reversal of the Examiner's rejection of claims 9-11 by the Board of Patent Appeals and Interferences (the "Board") is respectfully requested.

I. REAL PARTY IN INTEREST

The assignee, Sigma-Tu Industrie Farmaceutiche Riunite S.P.A., holds all rights in the subject invention as evidenced by the assignment recorded in the Patent and Trademark Office on October 14, 2004 starting at reel 015890 and frame 0553.

II. RELATED APPEALS AND INTERFERENCES

Appellants, their assignee, and the undersigned do not know of any prior or pending appeal, interference, or judicial proceeding which is related to, directly affects or is directly affected by, or has a bearing on the Board's decision in this appeal.

III. STATUS OF CLAIMS

Claims 9-11 stand rejected. They are at issue in this appeal and listed in the Claims Appendix.

Claims 1-8 were canceled without prejudice or disclaimer.

IV. STATUS OF AMENDMENTS

No amendment subsequent to the Office Action was filed.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The invention involved in this appeal is directed to treatment of uveitis with 3-(2-ethylphenyl)-5-(3-methoxyphenyl)-1H-1,2,4-triazole (see pending claim 9). Original claims 1 and 5; page 6, lines 13-15, of the specification; and page 13, line 4, to page 14, line 8 (the example entitled "Experimental Autoimmune Uveitis") of the specification support independent claim 9 as presented.

Dependent claims 10-11 are directed to particular embodiments of this invention which specify the subject who is being treated in claim 9. They are supported by original claims 7-8 and page 6, lines 23-24, of the specification.

Therefore, the invention as presently claimed is clearly supported by Appellants' disclosure as originally filed.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Under Section 103(a), was it proper to reject claims 9-11 as allegedly unpatentable?

VII. ARGUMENTS

35 U.S.C. 103 – Nonobviousness

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See id. ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue"). The use of hindsight reasoning is impermissible. See id. at 1397 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning"). Thus, a prima facie case of obviousness requires "some rationale, articulation, or reasoned basis to explain

why the conclusion of obviousness is correct." *Kahn* at 1335; see *KSR* at 1396. An inquiry should be made as to "whether the improvement is more than the predictable use of prior art elements according to their established functions." Id. But a claim that is directed to a combination of prior art elements "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id. Finally, a determination of prima facie obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 9-11 were rejected under Section 103(a) as allegedly being unpatentable over Mistrello et al. (Immunopharm. 10:163-169, 1985; hereinafter "Mistrello") and Hashimoto et al. (GB 2,246,350; hereinafter "Hashimoto") or alternatively Mistrello and Lenardo (WO 94/28926; hereinafter "Lenardo"). Appellants traverse because the cited documents fail to render obvious the treatment of uveitis with 3-(2-ethylphenyl)-5-(3-methoxyphenyl)-1H-1,2,4-triazole. If the compounds disclosed in Mistrello are not taught or suggested by Hashimoto or Lenardo for treatment of uveitis, why would it have been obvious for one of ordinary skill in the art to use Mistrello's compound to treat uveitis?

Mistrello discloses the claimed compound (ST1959/DL111-IT). It reports results on experimental models that can be predictive for the compound's therapeutic application in treating autoimmune diseases, organ transplantation, and cancer. The compound is administered to mice in the following concentrations: 1 mg/kg, 2 mg/kg, 5 mg/kg, 25 mg/kg and 100 mg/kg (see values in Tables I-VII). Mistrello is silent on uveitis.

The doses administered in Mistrello are higher than the dose (i.e., 0.25 mg/kg) that Appellants teach in the present specification. There is also no indication in Mistrello for the appropriate dose to treat uveitis. Therefore, how would one of ordinary skill in the

art know the effective amount to administer to treat uveitis from the teachings of the prior art?

Hashimoto discloses tricyclic compounds of the formula at page 2, lines 20-35, which have immunosuppressive activity (page 8, line 23). Hashimoto discloses that they can be used in the treatment of autoimmune diseases (page 8, line 29) including uveitis (page 8 line 32). But no pharmacologic data are reported and the only working example is a preparation method (from page 10, line 19, to page 12, line 21). Thus, Hashimoto is not enabling for the treatment of autoimmune diseases, more specifically uveitis, since they do not demonstrate pharmacologic effects and, thus, do not indicate that DL111-IT can be used for treating uveitis. Moreover, there is no indication in Hashimoto of what kind of modification to the extremely complex structure of the tricyclic compounds would maintain efficacy in treating uveitis. One of ordinary skill in the art reading Mistrello and Hashimoto would understand that a compound having immunosuppressive activity is not automatically effective in treating both immune and autoimmune diseases. An accurate reading of Mistrello reveals that DL111-IT, alias ST1959, the compound used in the present application is active in experimental models which might be of predictive value for its therapeutic application in clinical medicine (see "Discussion" section). One of ordinary skill in the art would weigh these words with great care since there was no clear teaching in the prior art that DL111-IT would be effective in treating uveitis. Common knowledge in the art of medicine has established that a potential candidate for use in medicine must demonstrate its efficacy in clinical study, as also established in USPTO practice. Laboratory animals are a valid model when tested on the same disease to be treated in humans. The authors of the Mistrello were very cautious in declaring clinical

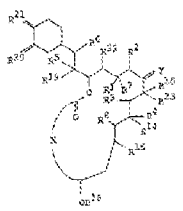
applications for DL111-IT because of such considerations. In fact, they demonstrated a clinical application only for skin graft rejection. The latter immune reaction, however, is not an autoimmune disease since the experimental model was carried out with an allo-graft. Therefore, Mistrello does not give a clear and unmistakable indication that DL111-IT would be effective in treating autoimmune disease, in particular uveitis.

Starting from Mistrello, one of ordinary skill in the art would search for help in the art. Hashimoto disclose tricyclic compounds with a chemical structure that is extremely far from DL111-IT. Hashimoto pronounces effectiveness of the tricyclic compounds as immunosuppressive agents. It discloses they are useful in the treatment of resistance to transplantation of organs or tissues, graft-versus-host diseases by medulla ossium transplantation, autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's diabetes, uveitis, such as Behcet's disease, etc. (Hashimoto, page 8, last paragraph). But there is no demonstration, much less animal testing, of any pharmacologic activity. Therefore, one of ordinary skill in the art would bear the burden of undue experimentation to test the compounds provided by Hashimoto with no reasonable expectation of success that they would effectively treat uveitis.

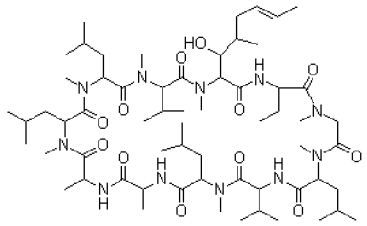
For this reason, Hashimoto does not remedy the deficiencies of Mistrello in failing to render obvious Appellants' claimed invention.

Moreover, the fact that Hashimoto discloses other immunosuppressive agents is irrelevant to constructing a prima facie case of obviousness because Hashimoto's compounds are not structurally related to the compound of the present invention. One of ordinary skill would find no guidance in Hashimoto on modifying the tricyclic compounds

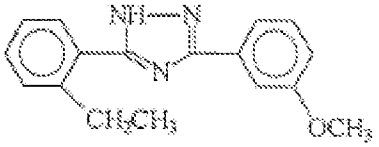
disclosed therein to arrive at the claimed DL111-IT compound. Hashimoto's compound is more similar to cyclosporin A than DL111-IT (see below).



Hashimoto



Cyclosporin A



DL111-IT = ST1959

From such a comparison, one of ordinary skill in the art would have been more likely to use a compound like Cyclosporin A than to DL111-IT in treating autoimmune disease. Cyclosporin A is specifically active in suppressing T-cell function (Mistrello et al., page 163, last paragraph of left column to first paragraph of right column). Instead, Appellants teach in the present applications that a compound is needed with specific and selective activity on T cells, in particular γδ T cells (see "Background" section). Therefore, based on the combination of Mistrello and Hashimoto, one of ordinary skill in the art would not have tried to use Hashimoto's compounds or even Cyclosporin A to treat uveitis with any reasonable expectation of success. Therefore, use of DL111-IT to effectively treat an autoimmune disease, specifically uveitis, would not have been obvious.

Lenardo discloses that autoimmune diseases can be treated by administering IL-2 (interleukin) together with the antigen which is specifically involved in the disease (page 1, lines 11-13). This treatment is to be practiced by a precise protocol comprising cyclic administration of the antigen, capable of challenging the T cell, then administering IL-2 when the T cell expresses high level of IL-2 receptors and, finally, re-administering the same antigen so as to cause T-cell apoptosis (programmed death) (see claim 2;

page 5, line 31; page 6, line 16). Lenardo reports a working example for experimental allergic uveitis (EAU) (page 39 of Example 3). This example emphasizes that only mice that were repetitively inoculated with IRBP (the protein which causes the onset of EAU) together with IL-2 were protected from the disease. Lenardo refers to the ability of co-administration of IL-2 and IRBP to prevent allergic uveitis. But IL-2 is a cytokine (i.e., a protein), whose structure is far different from the DL111-IT compound of the present invention. For this reason, the findings on IL-2 cannot be applied to DL111-IT. Moreover, IL-2 is effective only when it is co-administered with the antigen. In contrast, DL111-IT can be used alone (i.e., without antigen) to effectively treat uveitis.

Lenardo also teaches, "The key feature [...] is that only the antigen-specific T cells which are a small component of the patient's T cell repertoire would be eliminated. The treatment would leave the patient's immune system largely intact. This is in contrast to the present treatments that rely upon general immunosuppression that seriously incapacitates the host's immune function." Therefore, one of ordinary skill in the art, with the task of finding selective and less toxic immunosuppressants, as correctly stated by the Examiner on page 6 of the Office Action, would start from Lenardo, which is the most promising piece of art for treating uveitis. Lenardo teaches that general immunosuppression is to be avoided. In the search for an alternative treatment, one of ordinary skill in the art would not use Mistrello's compound because general immunosuppressive agents such as DL111-IT (the abstract teaches its "significant immunosuppressive activity both on humoral and cellular immunity") would not have been desirable according to Lenardo. Thus, it teaches away from the combination proposed by the Examiner.

Furthermore, one of ordinary skill in the art starting from Lenardo would never have arrived at the claimed invention, which does not provide a first challenge with the specific antigen, administration of the drug, and then second challenge with the same antigen. The claimed method only provides administration of the DL111-IT compound. Nothing in Lenardo suggests that the treatment could be successful by eliminating the administration of autoantigen. To the contrary, antigen administration is strictly necessary according to Lenardo. This also teaches away from Appellants' claimed invention.

Neither Hashimoto nor Lenardo fill in the gaps between Mistrello and the present invention. In view of the foregoing, claims 9-11 are patentable over Mistrello in view of Hashimoto or Lenardo.

A legal conclusion of obviousness is based on four factual findings: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. Here, the Examiner failed to make all of these factual determinations. Further, in determining the differences between the prior art and the claims, the Examiner must show that the claimed invention "as a whole" would have been obvious. *Schenck v. Nortron*, 218 USPQ 698 (Fed. Cir. 1983); *Stratoflex v. Aeroquip*, 218 USPQ 871 (Fed. Cir. 1983). Distilling an invention down to the "gist" or "thrust" of an invention disregards the requirement of analyzing the subject matter as a whole. *W.L. Gore & Associates v. Garlock*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983) (disregarding certain express claim limitations resulted in treating claims as though they read differently than allowed). The Examiner has not analyzed the claimed subject matter as a whole by ignoring the

failure of the prior art to teach or make obvious Appellants' use of DL111-IT compound to treat uveitis.

For the reasons provided above, the combination of cited documents does not render obvious Appellants' claimed invention. See independent claim 9. Moreover, claims 10-11 depending from the independent claim are also rendered obvious since the limitations of claim 9 are incorporated in the dependent claims. M.P.E.P. § 2143.03 citing *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988).

Appellants urge the Board to reverse the Section 103 rejection because the claimed invention would not have been obvious to one of ordinary skill in the art at the time it was made.

Conclusion

For the reasons discussed above, the Examiner's rejection is improper and it should be reversed by the Board. Appellants submit that the pending claims are in condition for allowance and earnestly solicit an early Notice to that effect.

Respectfully submitted,

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VIII. CLAIMS APPENDIX

9. (previously presented) A method for treating uveitis in a subject in need thereof, comprising administering 3-(2-ethylphenyl)-5-(3-methoxyphenyl)-1H-1,2,4-triazole to said subject.

10. (previously presented) The method of claim 9, wherein said subject is a mammal.

11. (previously presented)The method according to claim 9, wherein said subject is a human.

IX. EVIDENCE APPENDIX

None.

X. RELATED PROCEEDINGS APPENDIX

None.